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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/730,770	12/08/2003	Joost Dick de Bruijn	04148-00033	3424
22910	7590	06/17/2005	EXAMINER	
BANNER & WITCOFF, LTD. 28 STATE STREET 28th FLOOR BOSTON, MA 02109-9601			DUNSTON, JENNIFER ANN	
			ART UNIT	PAPER NUMBER
			1636	

DATE MAILED: 06/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/730,770

Applicant(s)

DE BRUIJN ET AL.

Examiner

Jennifer Dunston

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 March 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 08 December 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

AB

DETAILED ACTION

This action is in response to the amendment, filed 3/22/2005, in which claims 1, 3 and 7-17 were amended; claim 18 was newly added; and the specification was amended. Applicants' arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. New grounds of rejection are presented herein that were not necessitated by applicant's amendment of the claims since the office action mailed 10/22/2004. Therefore, this action is not final.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 102

Claims 1, 4, 5, 7, 8, 10-13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Walsh et al (Bone, Vol. 27, No. 2, pages 185-195, 2000) as evidenced by Cheng et al (Endocrinology, Vol. 134, No. 1, pages 277-286, 1994).

Walsh et al teach a method of determining the osteogenic potential of a population of cultured cells (e.g. paragraph bridging pages 192-193). Human bone marrow cells are obtained from patients undergoing thoracic surgery (e.g. page 186, *Subjects*). Cells are seeded at a density of 2×10^4 cells/cm² and cultured in standard medium consisting of Hepes-buffered Dulbecco's modified Eagle's medium (DMEM) supplemented with fetal calf serum, L-glutamine, penicillin, streptomycin, and L-ascorbic acid 2-phosphate (e.g. page 186, *Culture of human BMSCs*). The cells are cultured in the presence or absence of 10 nmol/L (10^{-8} M) dexamethasone (Dx) in standard medium (e.g. page 186, *Culture of human BMSCs*). Further, the cells are cultured in

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standard medium the presence or absence of FGF-2, a growth factor and an osteogenic stimulation factor (e.g. page 186, *Culture of human BMSCs*; paragraph bridging pages 189-190). Following the growth of cells, the alkaline phosphatase (AP) activity was determined using para-nitrophenyl phosphate (see Cheng et al, page 278, *Alkaline phosphatase assay* for assay conditions) and the following comparisons can be made: (i) cells grown in standard medium and cells grown in standard medium plus FGF-2 (e.g. page 186, *Cell Counting and Determination of AP Activity*; Figure 1), (ii) cells grown in standard medium and cells grown in standard medium plus Dx (e.g. Figure 2), (iii) cells grown in the standard medium plus FGF-2 in the presence or absence of Dx (e.g. Figure 2). Moreover, the anti-alkaline phosphatase monoclonal antibody from Hybridoma B4-78 is used for flow-cytometric analysis of cells grown in the standard medium, standard medium plus Dx, standard medium plus FGF-2, and standard medium plus Dx and FGF-2, where the presence of alkaline phosphatase indicates the presence of osteoprogenitor cells and maturing osteoblasts in the sample (e.g. page 186, *Antibodies*; Figure 4; Figure 5; page 190, paragraph bridging the left and right columns).

Claims 1-5, 7, 8, 10, 11, and 14-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Scheven et al (Journal of Bone and Mineral Research, Vol. 10, No. 6, pages 874-880, 1995; see the entire reference). **This rejection has been slightly altered to reflect the amendments to the claims.**

Scheven et al teach the establishment of human osteoblast cultures from trabecular bone explants of femoral heads obtained from orthopedic surgery (total hip replacement) patients (e.g. page 875, *Osteoblast cell culture and experimental set-up*). Explants are cultured in I-minimal

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essential medium (I-MEM) containing fetal bovine serum (FBS), glutamine and antibiotics (streptomycin, penicillin, and fungizone) (e.g. 875, *Osteoblast cell culture and experimental set-up*). Further, equal numbers of cells are cultured in the presence or absence of $1,25(\text{OH})_2\text{D}_3$ (vitamin D3) used at a concentration range from 10^{-10} to 10^{-5} M (e.g. page 875, *Osteoblast cell culture and experimental set-up*). The osteoblast differentiation parameters of cells grown in the presence and absence of vitamin D3 are compared using the following assays: (i) cellular alkaline phosphatase is assessed cytochemically using Naphtol AS-BI phosphate as a substrate and Fast Blue BB as a coupler, (ii) alkaline phosphatase activity is measured by incubating the cells in a solution containing p-nitrophenyl phosphate and quantifying the production of p-nitrophenol by measuring the absorbance at 405 nm, and (iii) osteocalcin is determined in culture medium (e.g. page 875, *Osteoblast differentiation parameters*; Table 1; Figure 2).

Claims 1-5 and 7-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Locklin et al (Cell Biology International, Vol. 23, No. 3, pages 185-194, 1999; see the entire reference).

Locklin et al teach the isolation of primary cultures of bone marrow cells obtained from patients undergoing total hip replacement surgery and the growth of the cultures in alpha-minimum essential medium containing fetal calf serum, penicillin and streptomycin (e.g. page 186, *Cell culture*). For the long-term growth of cells, 1×10^4 cells and grown under the following conditions: (i) without the addition of bFGF or Dex, (ii) in the presence of bFGF, (iii) in the presence of Dex Dex (Dexamethasone, 10^{-8} M), and (iv) in the presence of bFGF and Dex (e.g. page 187, left column; Table 1). After culture for 11 days, the alkaline phosphatase activity

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of the resulting colony forming units is determined and compared between groups (e.g. Table1; pages 189-190, bridging paragraph).

Claims 1, 3-8, 11, 14, 15 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Petite et al (Journal of Materials Science: Materials in Medicine, Vol. 7, No. 11, pages 665-671, 1996; see the entire reference) as evidenced by Leboy et al (Journal of Cellular Physiology, Vol. 146, pages 370-378, 1991; see the entire reference). **This is a new rejection.**

Petite et al teach a method of determining *in vitro* the capacity of a cell population to induce bone formation *in vivo* on artificial substrates, comprising (i) providing a cell population from human bone marrow, (ii) dividing the cell population into at least a first part and second part, (iii) culturing the first part in the presence of an osteogenic stimulation factor such as dexamethasone (Dex) and /or 1,25-dihydroxyvitamin D3 (vitamin D3), (iv) determining the degree of expression of a bone-specific protein such as alkaline phosphatase (ALP), and (iv) comparing the degrees of expression of the bone-specific protein of the first part and second part to evaluate the osteogenic capacity of the cells (e.g. paragraph bridging pages 665-666; page 666, 2.2 Bone marrow stromal cell isolation and culture, 2.7 Effects of Dex and 1,25(OH)D3; Figures 5 and 6). Petite et al teach the use of Dex and vitamin D3 at a concentration of 10^{-8} M (e.g. page 666, 2.7 Effects of Dex and 1,25(OH)D3). Petite et al teach the assay of cells cultured for 5, 10 and 20 days, which corresponds to about 1, 2 and 4 population doubling times (e.g. Figure 5; Abstract). Petite et al teach the use of culture medium comprising alpha-MEM further comprising serum and ascorbate (e.g. page 666, 2.2 Bone marrow stromal cell isolation and culture, 2.7 Effects of Dex and 1,25(OH)D3). Regarding the method of detecting alkaline

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phosphatase, Petite et al teach the use of the method of Leboy et al (e.g. page 666, 2.7 Effects of Dex and 1,25(OH)D₃). Leboy et al teach the quantitation of alkaline phosphatase by contacting the cells with a buffer containing p-nitrophenyl phosphate, a substrate for alkaline phosphatase, allowing the substrate to be converted to a reaction product, and detecting the reaction product in the presence of UV light (e.g. page 371, Alkaline phosphatase assay).

Claim Rejections - 35 USC § 103

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Walsh et al in view of Nefussi et al (The Journal of Histochemistry & Cytochemistry, Vol. 45, No. 4, pages 493-503, 1997; see the entire reference).

The teachings of the Walsh et al reference are described above and are applied as before.

Walsh et al do not teach the quantification of bone sialo protein or osteonectin expression.

Nefussi et al teach the isolation of rat calvaria bone cells, which are seeded at 2×10^4 cells in Dulbecco's modified Eagle's medium with fetal calf serum, streptomycin, and penicillin (e.g. page 494, Bone Cell Isolation and Culture). After 15 days, the cells are fixed and sectioned for detection of bone sialo protein (BSP) and osteonectin (ON) using an EM immunohistochemical procedure (e.g. page 494, EM Immunohistochemical procedure; Figure 1). Further, Nefussi et al teach the association of BSP and ON with the osteoid and the mineralized matrix formed by the cultured cells in a manner that duplicates what is observed during osteogenesis *in vivo* (e.g. Abstract; page 501, left column, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of determining the osteogenic potential of cells of Walsh et al to include the antibodies and detection methods taught by Nefussi et al because Walsh et al teach it is within the ordinary skill in the art to use antibodies to detect the mineralized matrix formed by the cultured cells.

One would have been motivated to make such a modification in order to receive the expected benefit of observing a phenotype *in vitro* that is an indicator of bone formation observed *in vivo*. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Walsh et al in view of Candeliere et al (Bone, Vol. 28, No. 4, pages 351-361, 2001).

The teachings of the Walsh et al reference are described above and are applied as before.

Walsh et al do not teach the quantification of bone sialo protein, osteocalcin, and osteopontin.

Candeliere et al teach the use of antibodies directed against alkaline phosphatase (ALP), bone sialo protein (BSP), osteocalcin (OCN) and osteopontin (OPN) to determine the expression pattern of each protein in sections of neonatal rat calvarial bone (e.g. page 352, left column, last full paragraph; pages 352-353, *Immunohistochemistry*). Further, Candeliere teach that all osteoblasts and preosteoblasts express ALP (e.g. paragraph bridging pages 353-354). Moreover, Candeliere et al teach the differential expression of BSP, OCN and OPN demonstrating that

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different subsets of preosteoblasts, osteoblasts and osteocytes express diverse gene profiles depending on their position within the developing clavaria (e.g. Tables 1, 2 and 3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of determining the osteogenic potential of a population of cultured cells of Walsh et al to include the antibodies taught by Candelieri et al because Walsh et al teach it is within the skill of the art to use antibodies to detect markers of osteogenic differentiation and because Candelieri et al teach the use of antibodies to further characterizing the cells of the osteoblast lineage.

One would have been motivated to make such a modification in order to receive the expected benefit of further characterizing cells differentiated *in vitro*. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments (35 USC § 102)

Applicant's arguments filed 3/22/05 have been fully considered but they are not persuasive. The response asserts that Walsh et al, Scheven et al and Locklin et al fail to teach or suggest each and every element of the claimed invention, that Scheven et al state that the "physiological and clinical relevance of our *in vitro* findings is not yet clear," and that the claims are novel over Walsh et al because the capacity of a cell population to form bone *in vivo* does not always correlate with *in vitro* expression of markers such as procollagen I (PCI), osteopontin (OP), or alkaline phosphatase (ALP) by the cell population.

The response asserts Walsh et al, Scheven et al and Locklin et al fail to teach or suggest each and every element of the claimed invention for the following reasons: (i) the references fail to assess *in vivo* the ability of their enriched cells to induce bone formation, and (ii) the references fail to correlate the degree to which cells respond to an osteogenic factor by expressing a bone-specific protein with the ability to induce bone formation *in vivo*. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., assessing the ability of cells to induce bone formation *in vivo* and correlating the degree to which cells express a bone-specific protein to the ability to induce bone formation *in vivo*) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The specification teaches the statistical analysis of the expression data comprising (i) calculating the logarithm of the ratio of the degrees of expression of the bone-specific protein of cells of the first part and the second part, and (ii) comparing the value obtained by the abovementioned calculation to a reference index, wherein a value larger than the index indicates a greater osteogenic potential for the cell population to induce bone formation *in vivo* (e.g. page 6, lines 22-30; page 7, lines 1-9). Although the specification teaches the importance of statistical analysis in comparing the degrees of expression, this method step is not recited in the rejected claims. The claims recite the method step of "comparing the degrees of expression of the bone-specific protein of the first part and the second part." Walsh et al, Scheven et al, and Locklin et al each teach the claimed method steps. Furthermore, the step of assessing the ability of cells to

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induce bone formation *in vivo* is not a limitation of the rejected claims. Thus, the deficiency of the references in this area is not at issue.

The response asserts that Scheven et al does not teach the *in vivo* ability of the cultured cells to form bone because Scheven et al state that the “physiological and clinical relevance of our *in vitro* findings is not yet clear.” This argument is not found persuasive because Scheven et al are referring the effect of methotrexate (MTX) on osteoblast proliferation and differentiation. This statement is not made with regard to the teachings of Scheven et al relied upon in the rejection. The teachings applied in the above rejection do not involve the use of MTX.

The response asserts that the claims are novel over Walsh et al because the capacity of a cell population to form bone *in vivo* does not always correlate with *in vitro* expression of markers such as procollagen I (PCI), osteopontin (OP), or alkaline phosphatase (ALP) by the cell population. However, the specification does teach that cells that express PCI, OP and ALP are capable of forming bone *in vivo* (e.g. page 14, lines 15-22). This is consistent with the teachings of Walsh et al. As described above, Walsh et al teach the presence of alkaline phosphatase in a population of cells indicates the presence of osteoprogenitor cells and maturing osteoblasts in the sample (e.g. page 186, *Antibodies*; Figure 4; Figure 5; page 190, paragraph bridging the left and right columns). Furthermore, Walsh et al teach that their results demonstrate the potential utility of multiparameter flow cytometry as an adjunct to the use of functional assay for the assessment of a cultured cell population’s osteogenic potential (e.g. paragraph bridging pages 192-193).

Therefore, the references applied under 35 USC § 102 meet each of the limitations of the rejected claims.

Response to Arguments (35 USC § 103)

Applicant's arguments filed 3/22/05 have been fully considered but they are not persuasive. The response asserts that Walsh et al fail to teach or suggest the claimed invention under 35 USC § 102 and that the secondary references fail to cure the deficiencies of Walsh et al. This is not found persuasive for the reasons set forth above with regard to the Walsh et al reference. Thus, the combination of Walsh et al and the secondary references meet each of the claim limitations for the rejected claim.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jennifer Dunston
Examiner
Art Unit 1636

jad


TERRY MCKELVEY
PRIMARY EXAMINER